Author's response to reviews

Title: Paraneoplastic Neuromyelitis Optica associated with ANNA-1 Antibodies in Invasive Thymoma

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Penny A. Asbell, M.D.

*BMC Ophthalmology*

RE: MS: 7296003521276708
Case report
Paraneoplastic Neuromyelitis Optica associated with ANNA-1 Antibodies in Invasive Thymoma

Dear Dr Asbell:

I thank the editors and reviewers of *BMC Ophthalmology* for taking their time to review our manuscript entitled "Paraneoplastic Neuromyelitis Optica associated with ANNA-1 Antibodies in Invasive Thymoma". Having gone over the suggested comments, I have made appropriate corrections and clarifications. Attached are the revised manuscript and the modified figure. Each of the coauthors has seen and agreed with the changes made to this revision. I hope the revised manuscript will better meet the publication requirement of *BMC Ophthalmology*.

Sincerely,

Jeong-Min Hwang, M.D.
Professor
Department of Ophthalmology
Seoul National University College of Medicine
Reviewer: Dr. Heather Moss

The authors present an interesting case that meets diagnostic criteria for NMO in association with malignant thymoma. The manuscript would benefit from expanded detail. My main concern is that the addition to the literature is incremental. In particular the association between Aqu-4 ab and thymoma and the the association of thymoma with multiple antibodies have been previously reported. Though the triad of Aqu-4, ANNA-1 and thymoma has not previously reported, the authors do not develop this contribution to make an educational or practice changing point. I defer to the editor regarding its suitability for BMC ophthalmology.

Major essential revisions

1. case presentation, paragraph 2, line 6-7, please detail type of color vision testing as many forms are not appropriate for use in a HM eye

   Changed as “She could not recognize the demonstration plate of Ishihara color vision test and any of the Hardy, Rand, and Rittler (HRR) color vision test with the right eye, but could recognize all of the Ishihara color vision test and HRR color vision test with the left eye.” (lines 66-69)

2. case presentation, paragraph 2, was any other testing done at this time besides MRI when the vision did not recover?

   She was lost to follow-up at this point and came back 5 months later when her left eye started to blur. Laboratory testing was not done as for the patient’s refusal.

3. case presentation, paragraph 3, was an MRI performed at time of presentation with left eye involvement?

   The following sentences were added. “MRI of the orbit and brain revealed high signal intensities of both optic nerves on T2-weighted images and increased abnormal enhancement of the right optic nerve extending to the prechiasmatic portion. However, there was no evidence of brain metastasis or CSF seeding.” (lines 84-87)

4. case presentation, paragraph 4, can you provide more details of the malignant epithelial neoplasm - was it histopathological similar identical to her prior thymoma? Was the biopsy tissue stained for AQU-4 antigen +/- antibody?

   Changed as, “Lung biopsy confirmed the diagnosis of a malignant epithelial neoplasm with cytokeratin expression, no epithelial membrane antigen, no CD5 expression, and no neuroendocrine marker expression. It was histopathologically similar to her prior thymoma and the possibility of recurrent thymoma could be
considered.” The biopsy tissue was not stained for AQU-4 antigen +/- antibody. (lines 89-94)

5. case presentation, paragraph 5, I suggest you say 'NMO spectrum' since she has not manifested spinal involvement.
- Yes. Changed as suggested. (line 109)

6. case presentation, paragraph 5, please provide more details regarding lower extremity symptoms - was additional imaging performed?
- The following sentences were added. “Neurologic examination revealed both lower extremity proximal dominant weakness of grade 4. Tingling sense below sensory level T10 developed with pain/temperature, vibration and positional sense hypesthesia. Whole spine MRI revealed longitudinally extensive transverse myelitis with central T2 high signal intensity of the spinal cord from level T3/4 to T11.” (lines 124-129)

7. Top of page 6 - suggest heading such as 'discussion'
- Changes as suggested with the heading of 'discussion' added. (line 131)

8. Discussion, last paragraph: AQU-4 is a known marker of poor visual recovery, so I think it is a stretch to suggest that this case illustrates a combination effect of both antibodies. Please scale this back.
- Changes as suggested to “The presence of paraneoplastic NMO-associated anti-APQ4 IgG in the serum may lead to a poor visual prognosis which is refractory to immunosuppressive treatment. However, the implication of the coexistence of ANNA-1 antibodies remains to be elucidated.” (lines 180-183)
The authors report a single case that potentially increases knowledge of autoantibodies associated with thymoma-related paraneoplastic disease, antineuronal nuclear antibodies type 1 (ANNA-1) as well as anti-aquaporin-4 antibodies (AQP4) being present in association with presumed neuromyelitis optica (NMO).

Major Compulsory Revisions

1. Case presentation paragraph 4
   a) More specific histopathological categorisation than “malignant epithelial” of the pulmonary neoplasm needs to be provided, especially that it was not a small-cell carcinoma.

   Changed as, “Lung biopsy confirmed the diagnosis of a malignant epithelial neoplasm with cytokeratin expression, no epithelial membrane antigen, no CD5 expression, and no neuroendocrine marker expression. It was histopathologically similar to her prior thymoma and the possibility of recurrent thymoma could be considered.” The biopsy tissue was not stained for AQU-4 antigen +/- antibody. (lines 89-94)

2. Case presentation paragraph 6
   a) It needs to be stated whether any abnormalities of the left optic nerve were identified on the follow-up MRI.

   “Follow-up MRI examination revealed contrast-enhancement in the left optic nerve.” (lines 118-119)

   b) More information including the results of spinal MRI needs to be provided to establish that the lower limb abnormalities were due to myelitis, peripheral neuropathy specifically needing to be excluded.

   “Whole spine MRI revealed longitudinally extensive transverse myelitis with central T2 high signal intensity of the spinal cord from level T3/4 to T11.” (lines 127-129)

3. Case presentation paragraph 3
   a) The timing of the optical coherence tomography (OCT) scans needs to be specified and if diffuse retinal nerve fibre layer atrophy in the left eye was present after only 1 week of loss of vision then it would need to be explained in the discussion.

   The timing of the optical coherence tomography was at 6 weeks after the onset of
visual loss in the left eye. We removed the sentence to the next paragraph.

b) There needs to be comment in the discussion about the multifocal ERG abnormalities. Was there retinal as well as optic nerve dysfunction, which would not be expected in NMO?

The outer retina and photoreceptor layers were relatively intact and standard electroretinograms were normal in both eyes. Multifocal ERG (mfERG) responses were slightly depressed in the center. However, for patients with poor fixation, the accuracy of mfERG results may be difficult to interpret. Particularly, central mfERG amplitudes are most affected by unsteady fixation as in our patient. (Chu PH, Chan HH, Leat SJ. Effects of unsteady fixation on multifocal electroretinogram (mfERG). Graefes Arch Clin Exp Ophthalmol. 2006;244(10):1273-82.) Therefore, there was no evidence to suspect retinal abnormalities. This was added in the discussion. (lines 138-145)

Minor Essential Revision
1. Discussion paragraph 1
a) What is the basis for saying that there was predominant involvement of the retinal ganglion cell layers?

The retinal nerve fiber layers showed severe thinning and retinal nerve fiber layers are the axons of retinal ganglion cells. “Our patient showed predominant involvement of the retinal ganglion cells associated with severe retinal nerve fiber layer thinning,” (lines 138-140)

Discretionary Revisions
1. Case presentation paragraph 2
a) There is a contradiction between the “total dyschromatopsia” in the right eye at first examination and the deterioration of colour vision during follow-up.

Thank your for your careful review. Changed as, “After 2 months, visual acuity and visual field defects of the right eye showed a further gradual deterioration without recovery and the patient was lost to follow-up.” (lines 73-75)

b) Was the abnormality of the right eye optic nerve on MRI contrast enhancement extending to the pre-chiasmatic portion?

Changed as, “Magnetic resonance imaging (MRI) revealed an abnormal contrast-enhancement of the right optic nerve extending to the prechiasmatic portion.” (lines 70-72)
2. Case presentation paragraph 3
   a) What is the meaning of “relatively normal” left optic disc?
      Changed as, “Funduscopy showed total pallor of the optic disc in the right eye, but
      a normal optic disc without edema or pallor in the left eye.” (lines 82-83)

3. Discussion, paragraph 1
   a) I think that the authors mean:
      “Thymoma has been associated with several immunologically mediated diseases
      and various paraneoplastic autoantibodies.”
      Changed as suggested. (line 132)
Reviewer: Dr. Eoin O'Sullivan
Reviewer's report:
The paper presents a very interesting case. However although it suggests a new association with a disease process the relevance to ophthalmology needs to be demonstrated by the authors.

Major Compulsory Revisions
1) Similar cases of patients with thymus disease and NMO have been previously described and so it seems the novel aspect of this case is the presence of ANNA-1 antibodies. However the clinical relevance to ophthalmology of this is unclear. Indeed the authors state that the ANNA-1 antibody ‘may not be directly related to the optic neuropathy’. If this is the case what is the relevance of this finding to an ophthalmology journal? Is such a finding not of more relevance to oncologists?

We agree with your point. However, the implication of the coexistence of ANNA-1 antibodies remains to be elucidated, especially in the context of optic neuropathy, and the report of original cases may serve as a basis for future research to extend our understanding of disease pathophysiology.

Minor Essential Revisions
2) Could the authors confirm that the lung lesion was a recurrence of the thymoma?

“Lung biopsy confirmed the diagnosis of a malignant epithelial neoplasm with cytokeratin expression, no epithelial membrane antigen, no CD5 expression, and no neuroendocrine marker expression. It was histopathologically similar to her prior thymoma and the possibility of recurrent thymoma could be considered.” (lines 89-94)

3) Why do they think the multifocal ERGs were abnormal?

“Multifocal ERG (mfERG) responses were slightly depressed in the center. However, for patients with poor fixation, the accuracy of mfERG results may be difficult to interpret. Particularly, central mfERG amplitudes are most affected by unsteady fixation as in our patient. Therefore, there was no evidence to suspect retinal abnormalities.” (lines 141-145)

4) The authors quote the paper by Wingerchuk et al regarding the diagnostic criteria for neuromyelitis optica. Did they use these? Should the diagnosis be one of neuromyelitis optica spectrum disorder?

Before the onset of LETM, the diagnosis would be NMO spectrum disorder. However, after the development of LETM and with the presence of AQP4 IgG, the
present case satisfies the diagnostic criteria of definite NMO.

5) The authors mention at the end of the case description that the patient suddenly developed limb weakness and paresthesia. Was the cause of this determined?

“Neurologic examination revealed both lower extremity proximal dominant weakness of grade 4. Tingling sense below sensory level T10 developed with pain/temperature, vibration and positional sense hypesthesia. Whole spine MRI revealed longitudinally extensive transverse myelitis with central T2 high signal intensity of the spinal cord from level T3/4 to T11.” (lines 124-129)